

Impact of Active Food Ingredients on Angiogenesis: A Comprehensive Review of Nutritional Activity, Source, Composition, and Mechanism of Action

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Abstract

The process by which endothelial cells from pre-existing capillaries, veins, and arteries divide to form new blood vessels is known as angiogenesis. Angiogenesis affects a wide range of physiological and pathological processes, such as the development of cancer and the course of atherosclerosis and other illnesses. The active elements in food have been shown in several studies over the past few years to have a little therapeutic effect as well as a regulatory influence on angiogenesis. Research on the effects of active food components on angiogenesis is crucial, considering the increasing interest in medical and food similarities. The pharmacological activity, source, composition, and mechanism of action of some of the active substances in therapeutic foods are covered in great detail in this article. It is crucial to investigate how active food ingredients affect angiogenesis, particularly in light of a growing curiosity in nutrition and health. Researchers provide extensive detail on the pharmacological activity, composition, source, and mechanism of action of some of the active substances that are included in therapeutic foods in this article. The aim of this article is to explore the impact of active food ingredients on angiogenesis by reviewing their nutritional activity, sources, composition, and mechanisms of action and to identify key food ingredients that influence angiogenesis, to examine the nutritional composition and bioactive properties of these ingredients, to understand the mechanisms through which these ingredients modulate angiogenesis. These might provide the groundwork for healthier food habits or help avert problems related to angiogenesis. This review may provide a conceptual framework for further research into and development of highly efficacious, low-toxicity anti-angiogenic drugs.

Keywords: Angiogenesis, endothelial cells, capillaries, veins, arteries, active food components, therapeutic foods, pharmacological activity, mechanism of action, pathological processes, cancer, atherosclerosis.

Introduction

Angiogenesis is a crucial process of life that creates new blood vessels from pre-existing ones. Angiogenesis is necessary to ensure the correct establishment of a functioning circulatory mechanism during the embryonic stage, which supplies nutrients and oxygen to every cell in the

human organism and ensures the removal of harmful substances therefrom each and every of individuals. In contrast, angiogenesis is limited to a few mature functions, including bone mending, wound recuperation, and ovulation. Angiogenesis is extremely tightly regulated and happens momentarily in each of these situations. Conversely, a multitude of disease scenarios are

distinguished by (and reliant upon) a chronic and dysregulated angiogenesis [1]. Numerous conditions that appear to have no relationship to one another are included in the wide variety of angiogenesis-dependent disorders, such as psoriasis, endometriosis, proliferative retinopathies, rheumatoid arthritis, and several cancers. The so-called angiogenic switch is "on" in many angiogenesis-dependent disorders because pro-angiogenic regulatory variables outweigh anti-angiogenic ones [2]. Conversely, there are additionally illnesses like ischaemic disorders that result in inadequate blood flow. In theory, substances that possess the ability to regulate the "on" or "off" state of the angiogenic valve may be considered as potential pharmacological agents for the management of disorders dependent on angiogenesis (anti-angiogenic compounds) or diseases with insufficient blood supply (pro-angiogenic compounds). This clarifies the reason the pharmaceutical business and academic organisations have been very interested in finding chemicals that modulate angiogenesis over the past 20 years [3,4,5]. A significant supply of naturally occurring bioactive chemicals with recently discovered modulatory effects on angiogenesis is now found in food and dietary components. Soy contains genistein [6], green tea contains abundant amounts of epigallocatechin 3-gallate [7], wine contains resveratrol [8], unfiltered coffee contains kahweol [9], virgin extra olive oil contains hydroxytyrosol and oleocanthal [10, 11], and rosemary extracts contain carnosol and carnosic acid [12], among other components. On the other hand, not much is known about food proteins and their possible role in controlling angiogenesis.

The Role of Dietary Components and Traditional Chinese Medicine in Modulating Angiogenesis for Cancer and Cardiovascular Disease Treatment

Numerous physiological and pathological conditions are indicated by angiogenesis, which

also serves as the underlying cause of numerous illnesses, including cancer, atherosclerosis, malignant tumours, and cerebrovascular disease [13]. Numerous factors, including transforming growth factor- β , platelet-derived endothelial growth factor, cyclooxygenase-2 (COX-2), hypoxia-inducible factor-1, vascular endothelial growth factor (VEGF), and VEGF receptor (VEGFR), are involved in the intricate process of angiogenesis. The primary angiogenic factor among them is VEGF, a homodimeric glycoprotein expressed by a single gene that can promote microvascular permeability and the migration, proliferation, and division of vascular endothelial cells. The primary way that food's active components control angiogenesis is through their impact on VEGF/VEGFR signal transduction. However, they can also have an anti-tumor angiogenesis effect by influencing VEGF/VEGFR. ..Over the last two decades, studies have demonstrated that angiogenesis in tumours is a major factor in their growth and that anti-angiogenesis is essential to preventing cancer growth, invasion, and metastasis [14]. Anti-angiogenesis is therefore a useful place to start when treating tumours. The anti-angiogenic and anti-tumor benefits of traditional Chinese medicine are being investigated and developed in a new field of inquiry brought out by the discovery of angiogenesis inhibitors and their concomitant clinical limitations [15]. In addition, it has been discovered that food and drug homologous foods promote angiogenesis in situations where endogenous repair and regeneration are insufficient to aid in the brain's recovery from cerebral ischaemia or brain injury brought on by cerebral ischaemia. In these situations, promoting angiogenesis can be a more effective solution, and food tonics can also be used to treat cerebrovascular and cardiovascular diseases. As a result, there are many opportunities for using food that promotes angiogenesis to treat tumour disorders, cardiovascular and cerebrovascular illnesses, and other conditions [16, 17].

Additionally, as time has gone on, researchers have discovered the active components in food that can help control angiogenesis; as a result, patients may find it simpler, safer, and more acceptable to treat their conditions nutritionally. Thus, the primary area of study in contemporary molecular medicine is the function of diet in the control of angiogenesis. The use of anti-angiogenics has gradually decreased as a result of contemporary clinical research that have demonstrated the clinical limits of the current angiogenic regulators, including brief therapeutic effects and unpleasant responses [18, 19]. The goal of the medical community's study has shifted throughout time to include studies on traditional Chinese medicine and the therapeutic qualities of food as a means of treating angiogenic disorders in a more effective and safe manner. The use of food as medicine has a lengthy history documented in historical accounts. The Yellow Emperor's Classic of Internal Medicine makes reference to the idea of "medicine and food homology"[20,21].

Impacts of Angiogenesis on Placental Development and Fetal Growth: Insights into Preterm Delivery, Pre-Eclampsia, and Intrauterine Growth Restriction

Vasculogenesis and angiogenesis are two processes that the placenta experiences at high levels throughout foetal development. Pregnancy success depends on the development, maturation, and maintenance of the placental vasculature. Preterm delivery, pre-eclampsia, and intrauterine growth restriction (IUGR) are among the obstetrical difficulties that women may face during pregnancy. These issues are mostly caused by an imbalance in human placental angiogenesis [22, 23]. A growing body of research indicates that IUGR may be linked to compromised angiogenesis at the fetal-maternal interface and/or reduced placental blood flow [24, 25]. Based on the nature of the vascular tree, previous research on IUGR placentas has demonstrated that the development of

terminal villi in IUGR placentas was much lower than that in normal term placentas [26]. In order to satisfy the needs of foetal growth and development, there must be enough space for material exchange, which is made possible by the placenta, an essential organ that connects the mother and foetus. Mammalian placentas and foetal and maternal blood do not directly touch, despite their morphological categorisation into several forms (e.g., hemochorial and epitheliochorial placentas) [27]. The pig placenta, for instance, is of the epitheliochorial type, with six layers of tissues separating the foetus from the mother's blood and its surface linked to the endometrium [28]. The biological process of creating new blood vessels from pre-existing ones is known as angiogenesis [29]. Furthermore, given that the placenta, fetal-maternal boundary, endometrium, and material exchange all undergo substantial angiogenesis. In order to satisfy the needs of foetal growth and development, there must be enough space for material exchange, which is made possible by the placenta, an essential organ that connects the mother and foetus. Mammalian placentas and foetal and maternal blood do not directly touch, despite their morphological categorisation into several forms (e.g., hemochorial and epitheliochorial placentas) [27]. The pig placenta, for instance, is of the epitheliochorial type, with six layers of tissues separating the foetus from the mother's blood and its surface linked to the endometrium [28]. The biological process of creating new blood vessels from pre-existing ones is known as angiogenesis [29]. Furthermore, given that the placenta, the fetal-maternal border, and the endometrium all undergo extensive angiogenesis and that the capillary network in the placental cotyledons facilitates the material exchange of foetal and maternal blood, it is obvious that angiogenesis is the primary biological event in the placenta that affects foetal development. All things considered, during pregnancy, the extent of vascularization, blood flow, and the ability of the fetal-maternal interface to exchange materials are

significant elements influencing foetal development, particularly angiogenesis, which is a crucial aspect of this biological event[30].

Food Substances having Therapeutic Effects that Control Angiogenesis

Flavonoids

Naturally occurring compounds or secondary plant metabolites, flavonoids have a 2-phenylchromone structure [31]. Their pharmacological properties are diverse, including beneficial effects on the central nervous system and cardiovascular system as well as anti-inflammatory, antibacterial, and anti-tumor properties. Some studies have shown that flavonoids can regulate and promote angiogenesis, including angiogenesis that is anti-tumor. The anti-tumor angiogenesis pathway involves the down-regulation of VEGF, COX-2, angiotensin-2, matrix metalloproteinases (MMP), an endogenous proteolytic enzyme, and other components. Figure 1B illustrates the anti-tumor

mechanisms of angiogenic regulating factors. It has been shown that angiogenesis is regulated by the flavonoids found in certain medicinal plants. For instance, used corneal neovascularisation models from rabbits and zebrafish embryos to study the inhibitory effect of isoliquiritigenin on angiogenesis [32]. In a distinct study, the anti-angiogenic activity and mechanism of puerarin glycosides (PGs) were ascertained by means of the scratch, migration, lumen formation, and cell cycle arrest tests. A range of PG concentrations (100 $\mu\text{g ml}^{-1}$, 200 $\mu\text{g ml}^{-1}$, and 400 $\mu\text{g ml}^{-1}$) were concurrently administered to MDA-MB-231 cells and human umbilical vein endothelial cells (HUVECs). Tubulin is an essential cytoskeleton component whose disordered polymerisation prevents the cell cycle from progressing. The expression of α -tubulin mRNA was determined by RT-PCR-western blot and primary antibodies such as α -tubulin, β -actin, cyclin A1, and CDK2. The findings showed that PGs have anti-angiogenic and cell cycle inhibitory activities, and they may induce MDA-MB-231 cells to reach Sphase arrest [33].

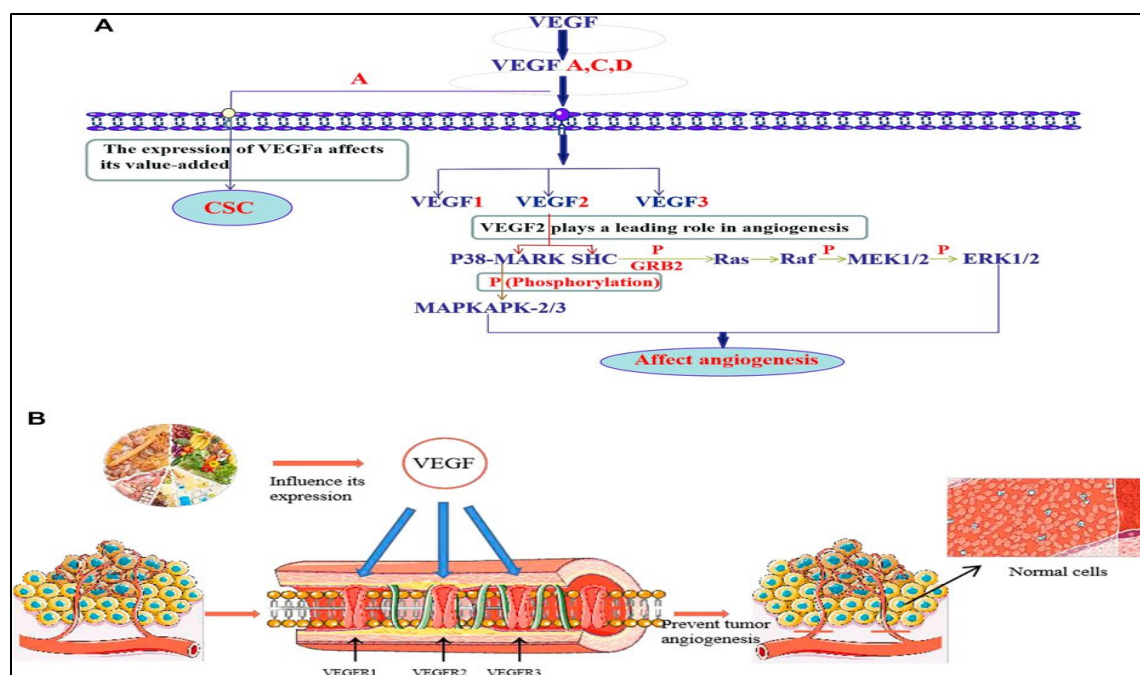


Figure 1 Structure of certain flavonoids influencing angiogenesis in medicinal food[32].

Terpenoids

Terpenoids are naturally occurring hydrocarbons that are found throughout the environment. They can be linked in a number of ways by isoprene or isopentane units. It has been demonstrated that terpenoids of all kinds are strong chemical building blocks with significant anti-disease and anti-treatment capabilities. They have potent anticancer effects in particular. They could be used as lead molecules to make new, secure, and efficient anticancer drugs. Additionally, studies have shown that some terpenoids are helpful in the treatment of cardiovascular diseases and have the capacity to regulate angiogenesis. Therefore, further investigation into the regulation of terpenoids' angiogenesis has great promise for the development of new anti-tumor drugs as well as for

the treatment of diseases associated with angiogenesis [33]. Using the biological model of zebrafish, researchers have examined the effects of curcuminol on the vascular development of embryonic bodies, the vascular regeneration of adult fish after they cut their tails, and the tissue regeneration of larvae after they cut their tails. Relative quantitative fluorescence PCR was used to determine the expressions of the VEGF and VEGFR2 genes. In order to do this, zebrafish embryos were given several doses of curcuminol (1 mg L⁻¹, 5 mg L⁻¹, 10 mg L⁻¹, 20 mg L⁻¹, and 50 mg L⁻¹). The results showed that 20 mg L⁻¹ increased the vascular endothelial growth of zebrafish embryo internodes, whereas 50 mg L⁻¹ increased VEGFR2 development in zebrafish embryos. Moreover, 1 mg L⁻¹ curcuminol had the greatest effect on tissue regeneration [34].

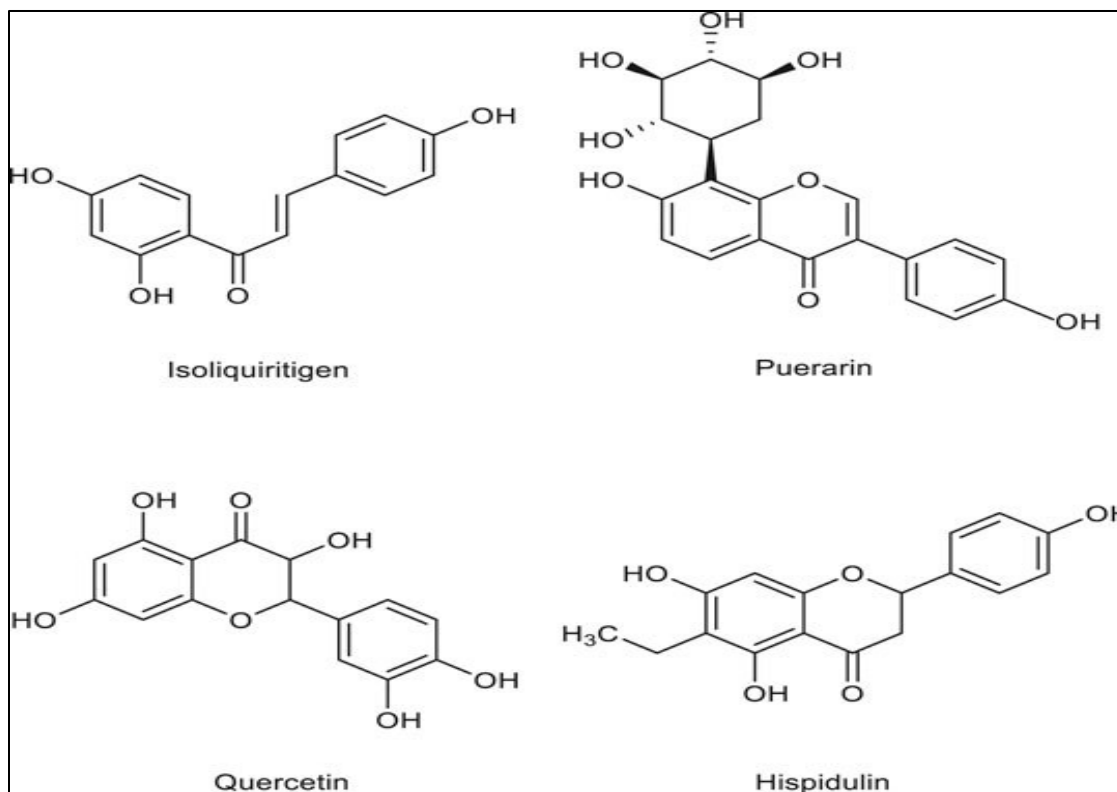


Figure 2 Structure of certain terpenoids influencing angiogenesis in medicinal food[34].

Saponins

Glycosides known as saponins are frequently found in nature, most notably in the monocotyledons and dicotyledons. They consist of triterpenoids or spiral sterane molecules. Saponins have significant physiological and pharmacological roles. Over the past few years, angiogenesis regulators have been the focus of intense research into natural medicine sources. In tests using animal models, saponins—naturally occurring active compounds found in food—have been demonstrated to be safe and effective in regulating angiogenesis. The saponins that regulate angiogenesis, as well as several saponin structures, are shown in. In several investigations, the rats were split into four groups: one for a sham surgery, one for an acute myocardial infarction control, one for ginsenoside Rg1 low-dose therapy (1 mg kg⁻¹), and one for high-dose treatment (5 mg kg⁻¹) [35].

Polysaccharides

Usually consisting of hundreds or even tens of thousands of individual sugar molecules, polysaccharides have a comparatively high molecular weight. Compounds having ten or more solitary sugar molecules polymerised by a glucosidic bond are what they are called. Significant biological macromolecules known as polysaccharides are found in huge quantities in plants, microorganisms, and animals. Polysaccharide biological activities have attracted a lot of attention recently in biochemical and medical research because of their immunomodulatory qualities. Polysaccharides have a wide range of biological activity, low toxicity, and encouraging potential as building blocks for the development of medicinal compounds. They may thus be useful in the treatment of angiogenic diseases [36].

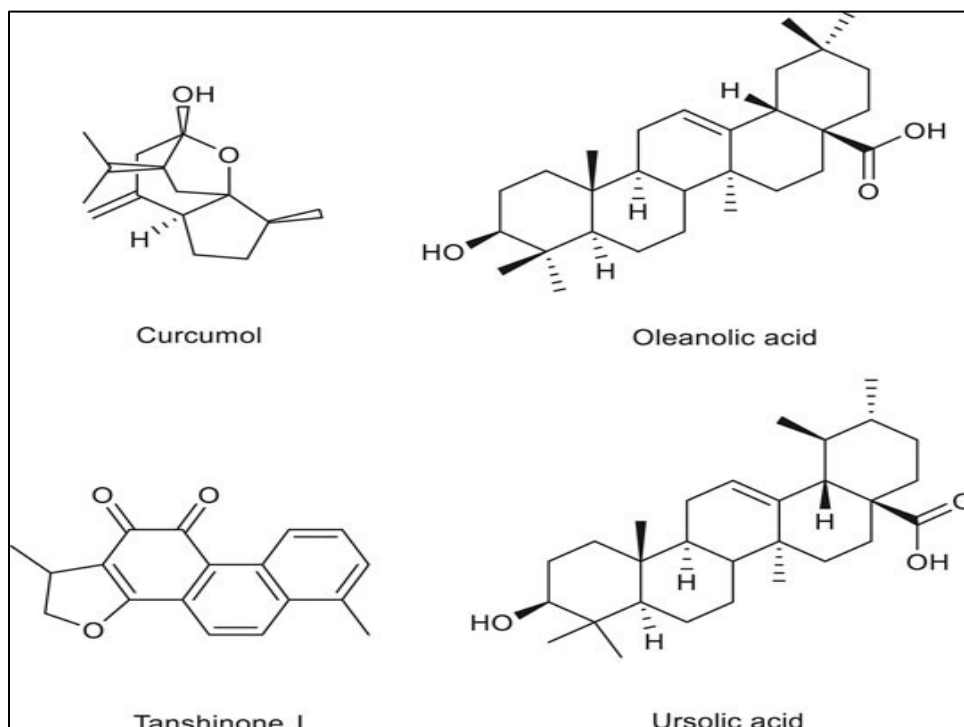


Figure 3 Structure of certain saponins influencing angiogenesis in medicinal food.[35].

Alkaloids

Alkaloids are a naturally occurring organic chemical family that includes nitrogen and is mostly produced by plants. The majority of alkaloids have complex ring structures to which the nitrogen atoms are bound. In addition, most alkaloids are basic, have significant biological activity, and are important pharmacologically active components in therapeutic diets. Plant alkaloids have been demonstrated to possess a wide range of anti-tumor and anti-angiogenesis properties and may be obtained from several sources. They can therefore be used to treat a range of clinical problems. In one study, the scientists isolated, purified, and identified the active ingredients in *Evodia rutaecarpa* fruit. Nine of them were revealed to have an inhibitory effect on angiogenesis using the experimental model zebrafish [37].

Polyphenols

Tannins, another name for polyphenols, are important natural chemicals found in abundance in plants. Because of the complex structure, many homologous molecules, and active chemical properties of polyphenols, research on them has

progressed fairly slowly. Nevertheless, advances in polyphenol chemistry over the past 30 years have allowed for a full understanding of the molecular structure and properties of polyphenols. Among their many other routes of action, plant polyphenols are recognised as safe anti-tumor medications that impact tumour angiogenesis. Furthermore, polyphenols have antioxidant, anti-inflammatory, anti-mutagenic, and anti-cancer properties that protect the human genome and prevent disease. As a result, the polyphenols present in specific foods may be used as therapeutic agents [38]. Emodin's effect on hepG2 cell angiogenesis has been investigated in relation to human liver cancer. To do this, the effects of rhein, HIF1A, and VEGF on HepG2 cells as well as rhein's anti-hepatoma characteristics were examined using an *in vivo* chicken CAM model. The experimental groups were randomly allocated to include a negative control group (normal saline), low-dose ($10 \mu\text{mol L}^{-1}$) and high-dose ($20 \mu\text{mol L}^{-1}$) emodin groups, and a positive control group (0.15 mg L^{-1} ; dexamethasone). By using *in vitro* culture methods, it was discovered that emodin inhibits CAM angiogenesis. For this reason, COCl₂ treatment was used to simulate chemical hypoxia in HepG2 cells [39].

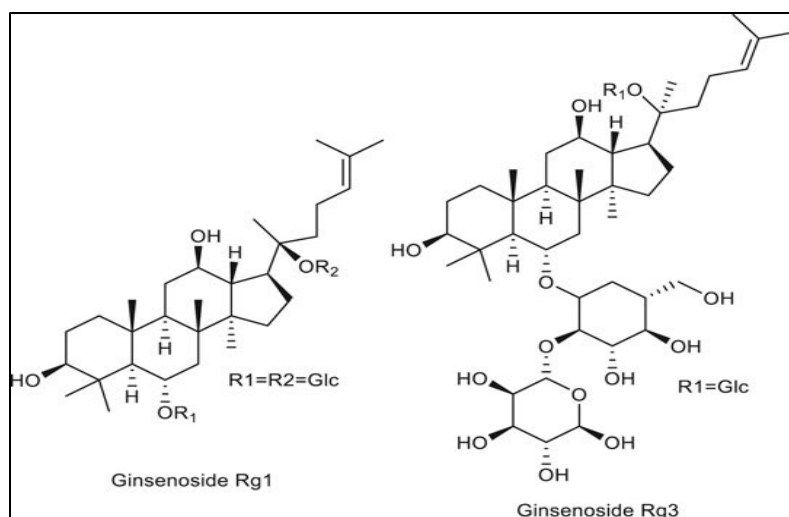


Figure 4 Structure of certain alkaloids influencing angiogenesis in medicinal food. [37].

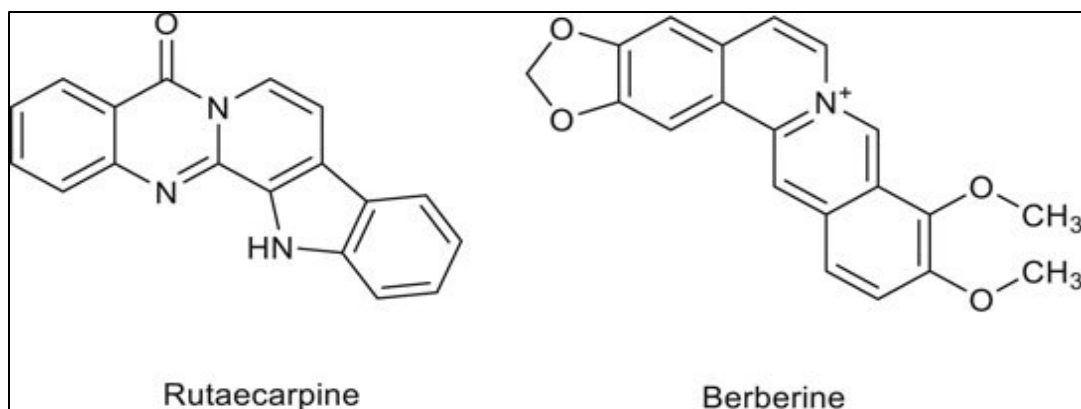


Figure 5 Structure of certain polyphenol influencing angiogenesis in medicinal food [39].

Additional Compounds

The impact of black garlic on angiogenesis is one instance. In one research, the authors created transgenic zebrafish in vivo and HUVEC in vitro to examine the impact of black garlic on angiogenesis. As an in vivo assessment model, the transgenic zebrafish Flk-1: GFP labelled with green fluorescent protein was employed. The groups that were developed were the vascular model group (0.2 $\mu\text{g ml}^{-1}$ PTK787), blank control group, experimental group, and control group. The black garlic extract treatment group (concentration gradient of 0.2 $\mu\text{g ml}^{-1}$, 0.8 $\mu\text{g ml}^{-1}$, 3.2 $\mu\text{g ml}^{-1}$, and 3.5 $\mu\text{g ml}^{-1}$ PTK787) and positive control group (30 $\mu\text{g ml}^{-1}$ Danhong injection and 0.2 $\mu\text{g ml}^{-1}$ PTK787) were cultivated under standard conditions. The findings shown that black garlic extract may, in a dose-dependent way, increase the number of embryonic internodes vessels and small intestine veins while also markedly improving the pathological alterations of embryo internodes and

lower intestinal veins caused by PTK787. PTK787 suppressed the number of embryonic internodes vessels inferior intestine veins to normal when the quantity of black garlic extract rose to 3.2 $\mu\text{g ml}^{-1}$. Moreover, in a dose-dependent way, black garlic extract may strengthen HUVEC's activity and encourage its proliferation. The aforementioned findings demonstrated that black garlic might stimulate the HUVEC pathway, thereby boosting angiogenesis [40]. The impact of Dalbergia odorifera extract on angiogenesis was investigated in a different investigation. .. The outcomes demonstrated that the transgenic zebrafish capillary germination was positively impacted by the Dalbergia odorifera B3 extract, with the greatest effect occurring at 30 $\mu\text{g ml}^{-1}$. These findings suggest that Dalbergia odorifera B3 extract can enhance angiogenesis and mitigate vascular damage caused by VEGFR kinase inhibitor II; the mechanism behind this effect is associated with the upregulation of VEGFR mRNA expression [41].

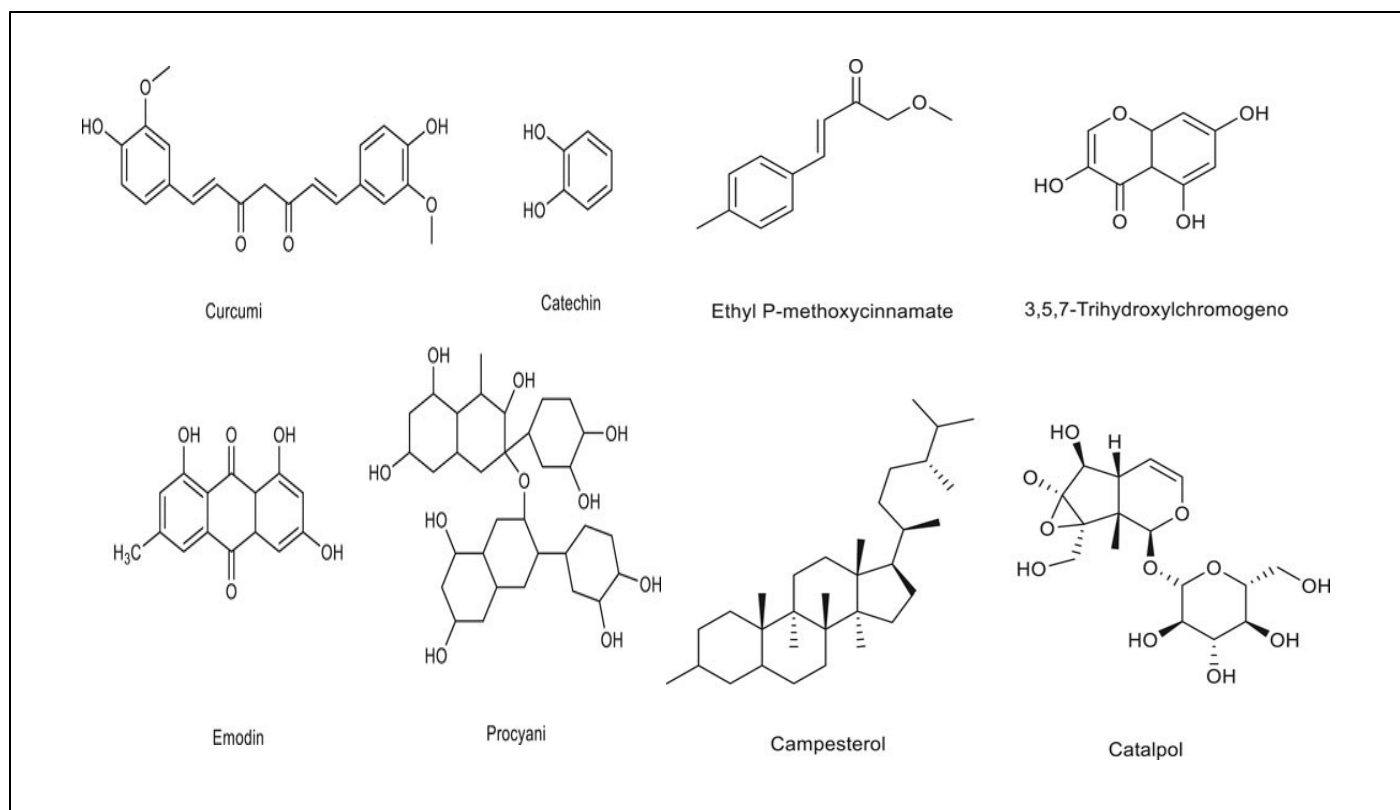


Figure 6 Structure of certain Other active compounds influencing angiogenesis in medicinal food [42].

The Mechanism by Which Medicinal Food Regulates Angiogenesis

Numerous diseases have been linked to angiogenesis, according to studies. When it comes to the control of angiogenesis, the active ingredients in medicinal foods mostly work by changing the appropriate signal transduction pathways to either promote or inhibit angiogenesis. The two primary regulatory factors whose signal transduction is impacted are VEGF and VEGFR, which promote regulatory effects. Vascular permeability factor, or VEGF, is one of the main growth factors involved in both healthy and pathological angiogenesis. This component may lead to increased angiogenesis and vascular hyperpermeability and is seen in a large number of human tumours. Certain tumours can be prevented from growing by blocking VEGF expression using antibodies or antisense tactics; overexpression of VEGF promotes carcinogenesis [43].

Mode of Regulation of Angiogenesis Inhibition

The primary method by which the active ingredients in medicinal foods prevent angiogenesis is by blocking the appropriate angiogenesis signal's transduction pathway. It can be used to treat a few other disorders caused by angiogenesis; however it primarily targets tumour angiogenesis. Since research shown that the vasculature is necessary for tumour growth, controlling tumour vascular expansion and angiogenesis has been the primary focus of tumour therapy. One of the main ways that dietary active ingredients inhibit angiogenesis is by controlling angiogenic factors and vascular endothelial cell proliferation and migration. The precise mechanisms involve direct inhibition of vascular endothelial cell migration and proliferation, inhibition of extracellular matrix metalloproteinase (MMP) activity, inhibition of tumour angiogenic factors' signal transduction, and

promotion of tumour angiogenesis inhibitors' expression [44]. Numerous studies have demonstrated cancer carcinogenesis is inhibited when overall food consumption or energy intake is restricted. To inhibit tumour angiogenesis, curcumin from *Curcuma longa* extract inhibits the proliferation of vascular endothelial cells and the expression of factors that promote angiogenesis; rosmarinic acid extracted from rosemary inhibits angiogenesis and achieves an anti-tumour effect by inhibiting VEGF expression and IL-8 release from related cells [45,46]. Chlorogenic acid from *Lonicera japonica* extract, for example, can inhibit the expression of MMP-9 and MMP-2 by down-regulating the COX-2-MMP signalling pathway.

Regulatory Mechanisms for Promoting Angiogenesis

Recent research has demonstrated that VEGF can control thrombosis, enhance vascular permeability, and stimulate endothelial cell division and proliferation. Consequently, there exists a tight correlation between VEGF and the onset and progression of certain cardiovascular disorders [47]. Ethyl p-methoxycinnamate and ethyl trans-p-methoxycinnamate, the active ingredients isolated from *Kaempferia galanga*, are utilised to treat angiogenic disorders by preventing bFGF-induced angiogenesis and inhibiting the tyrosine kinase inhibitor of angiogenesis [48]. The primary method of treating cardiovascular disorders is to encourage angiogenesis. For instance, by increasing HIF1A activity, ginsenoside Rb1 enhances angiogenesis and cardiac function. *Rehmannia glutinosa* extract contains catalpol, which can stimulate the Notch1 signalling pathway, endothelial progenitor cells, and angiogenesis while preventing myocardial infarction [49]. In addition to treating tumours and cardiovascular conditions, the active dietary component-induced angiogenic regulation offers therapeutic benefits for other angiogenesis-related disorders as well, such as aiding in the healing of wounds on the skin and blood vessel-related

conditions affecting the eyes. It has been discovered that beta-sitosterol, an active ingredient in aloe vera, facilitates angiogenesis, which in turn promotes wound healing. Asiaticoside increases the amount of VEGF, which facilitates skin wound healing. Fucoidan has the ability to prevent VEGF from attaching to its cell surface receptors, which inhibits chemotaxis and mitosis of VEGF165 in HUVEC. It also inhibits VEGF production, which has an anti-coagulant action [50,51].

Placental Angiogenesis: The Regulatory Impact of Functional Nutrients

Fatty acids have also been shown in an increasing number of studies to be crucial in controlling angiogenesis in tumours and other organs, such as the placenta. Other fatty acids can be progressively synthesised from essential fatty acids, which include linoleic acid and α -linolenic acid, which belong to the n-6 (ω -6) and n-3 (ω -3) families, respectively. They are essential to the body's biological processes because they affect the composition and operation of cell membranes, control the expression of genes involved in cell homeostasis, and serve as building blocks for a few signalling molecules [52]. Furthermore, for dietary essential fatty acids, such as linoleic and α -linolenic acid, to have their full biological effects, the body must convert them into their long-chain metabolites. Generally speaking, n-3 long-chain polyunsaturated fatty acids (LCPUFAs), which include EPA and DHA, are thought to have strong antiangiogenic properties in cancer cells and other cell systems, preventing the synthesis of several significant angiogenic factors, including NO, PGE2, VEGF, and platelet-derived growth factor [53]. In the meantime, n-6 LCPUFAs, such as arachidonic acid (AA or ARA), have proangiogenic properties that boost angiogenesis, increase endothelial cell motility and proliferation, and encourage the production of angiogenic growth factors. In addition to their antiangiogenic

properties in cancer cells, n-3 LCPUFAs have been demonstrated to downregulate VEGFR-2 in endothelial cells, therefore attenuating the VEGF signal during normal physiological angiogenesis [54].

In general, n-3 long-chain PUFAs (LCPUFAs), including EPA and DHA, are generally supposed to have potent antiangiogenic effects in cancer cells and other cell systems, inhibiting the production of many important angiogenic factors, such as VEGF, platelet-derived growth factor, PGE₂, and NO [53]. Meanwhile, n-6 LCPUFAs, including arachidonic acid (AA or ARA), have proangiogenic effects, encouraging the transcription of angiogenic growth factors, increasing the migration and proliferation of endothelial cells, and promoting angiogenesis. Apart from an antiangiogenic role in cancer cells, in normal physiological angiogenesis, n-3 LCPUFAs are also shown to downregulate VEGFR-2 in endothelial cells, thus weakening the VEGF signal [54]. A large number of cell experiments in vitro have shown that EPA and

DHA can significantly suppress the proliferation, migration, and tubule formation of endothelial cells, indicating the antiangiogenic effect of n-3 fatty acids. These fatty acids can influence angiogenesis via a variety of mechanisms. In addition to regulating the expression of the aforementioned angiogenic factors, they can also affect the expression of other regulatory factors, such as eicosanoids, cyclo-oxygenase, fatty acid-binding proteins (FABPs), and NO[55].

Numerous in vitro cell tests have demonstrated that EPA and DHA may effectively inhibit endothelial cell proliferation, migration, and tubule formation, demonstrating the antiangiogenic properties of omega-3 fatty acids. These fatty acids have a number of ways in which they might affect angiogenesis. Apart from controlling the expression of the previously described angiogenic factors, they have the ability to influence the expression of other regulatory factors including NO, cyclo-oxygenase, eicosanoids, and fatty acid-binding proteins (FABPs)[55].

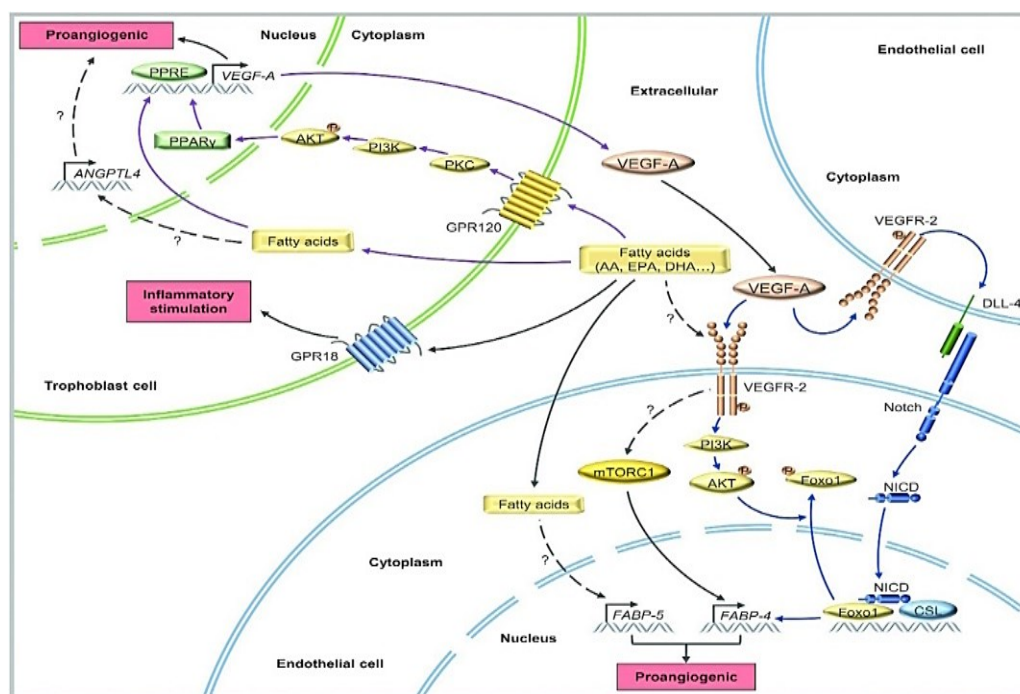


Figure 7 The proposed molecular mechanisms by which fatty acids regulate placental angiogenesis[55].

Diseases Associated with Angiogenesis

The growth of arteries is essential to the maturation of the placenta, the embryo, wound healing, tissue reorganising, recuperation, and bioengineering [56]. Angiogenesis, which follows vasculogenesis in the development of an embryo, is necessary for the correct formation of a working circulatory system that supplies oxygen and nutrients to every cell in the body and for the elimination of waste products [57]. On the other hand, angiogenesis is linked to very few biological processes in adults, including as the reproductive cycle, wound healing, and bone regeneration. Angiogenesis is momentary and delicately controlled by the ratio of favourable-to antiangiogenic factors in each of these processes. However, dysregulated neovascularisation has been linked to a number of viral, ischaemic, carcinogenic, and inflammatory disorders [58]. A number of conditions that don't seem to be connected are on the list of angiogenesis-dependent

illnesses, such as proliferative retinopathies, rheumatoid arthritis, psoriasis, endometriosis, and the majority of malignancies. An excess of pro-angiogenic regulatory factors relative to anti-angiogenic ones is seen in several angiogenesis-dependent illnesses.

Antiangiogenic Strategies Using Nutraceuticals

This section contains studies on recently identified antiangiogenic nutraceuticals that have been suggested as preventive and therapeutic measures in various illnesses that frequently include an environment of oxidative stress and inflammation. A brief list of foods with the main nutraceutical ingredients that have been demonstrated to have antiangiogenic effects is provided. See details in [59] for the average concentration of each active chemical and the particular antiangiogenic mechanism in experimental models.

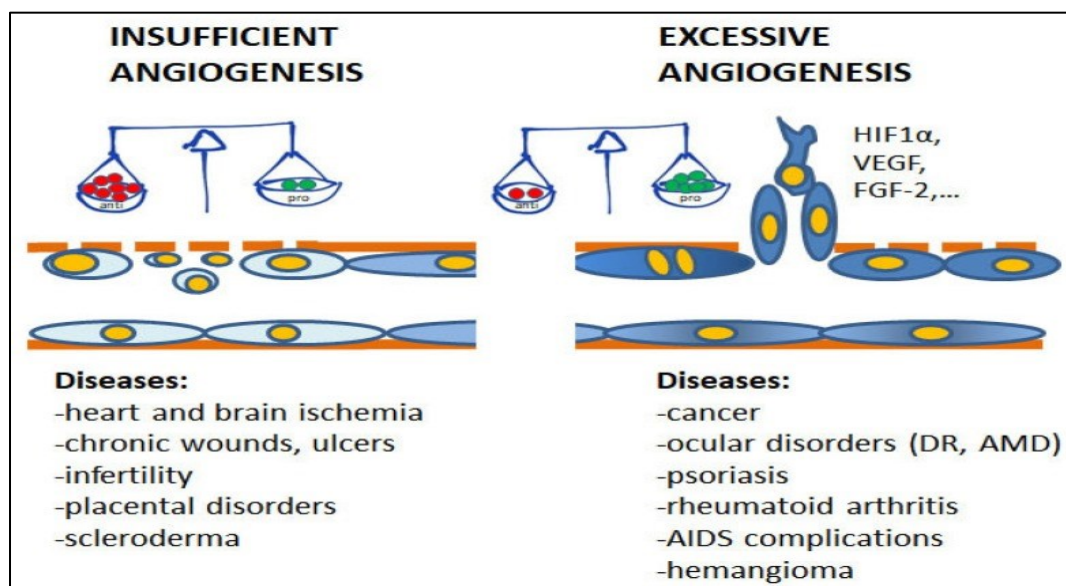


Figure 8 The role of both excessive and inadequate angiogenesis in many clinical conditions. The imbalance between favourable- and antiangiogenic compounds, which is brought on by hypoxia, diseases of metabolism, autoimmune diseases, and oxidative damage, is the fundamental cause of the angiogenesis result. (Age-related retinal deterioration; AMD, diabetic retinopathy)[58].

Category	Food	Active Principles
<i>Beverages and drinks</i>	Green tea, red wine	Stilbenoids (resveratrol), flavanols (catechins)
<i>Fruits</i>	Strawberries, blackberries, raspberries, blueberries, cranberries, apple, pineapple, cherries, oranges, grapefruit, lemons, red grapes, pomegranate	Carotenoids (lycopene), the most part of flavonoids and in particular glycosides of anthocyanidins (anthocyanins), stilbenoids (resveratrol), flavanones (hesperetin),
<i>Vegetables and mushrooms</i>	Soy beans, artichokes, tomatoes, garlic, kale, broccoli, cauliflower, Brussels sprouts, bok choy, lavender, maitake mushrooms, parsley, pumpkin	Flavones (apigenin), isoflavones (genistein), flavonols (quercetin), isothiocyanate (sulfurafane), glycosides of anthocyanidins (anthocyanins)
<i>Oils</i>	Extra-virgin olive oil, grapeseed oil	Oleic acid, phenylethanoids (hydroxytyrosol)
<i>Other</i>	Dark chocolate, ginseng, licorice, turmeric, ginger, nutmeg, cinnamon, red propolis	Glycosides of anthocyanidins (anthocyanins), ginsenosides, phenolic acids (curcumin)
<i>Fish and meat</i>	Tuna, sea cucumber	Omega-3 fatty acids, mucopolysaccharides, saponins

Table 1 Antiangiogenic foods with their main active principles[59].

Societal Effects of Active Food Ingredients on Angiogenesis: Impact on Different Populations

❖ Adults

Flavonoids, polyphenols, and omega-3 fatty acids are examples of active food elements that influence angiogenesis and have been associated with a number of cardiovascular and metabolic advantages in adults. By regulating blood vessel creation, these substances enhance circulation and may lower the risk of long-term conditions including heart disease and stroke. These components' capacity to alter angiogenesis may also aid in tissue regeneration and repair, especially following surgery or injury [60,61].

❖ Children

A child's growth and development, particularly the formation of vascular networks, are greatly influenced by their diet. Vitamin C, flavonoids, and folate are a few nutritional elements that support healthy organ and tissue development by promoting endothelial cell activity and capillary expansion. Additionally, early childhood angiogenesis might affect immunological function and developmental milestones, which can have an effect on long-term health [62].

❖ Pregnant Women

Angiogenesis is essential for both fetal growth and placental development throughout pregnancy. Angiogenesis is known to be influenced by nutrients including folate, omega-3 fatty acids, and antioxidants, which provide appropriate blood flow to the placenta and support fetal development. Preeclampsia, gestational diabetes, and limited fetal growth are among the issues that can result from inadequate angiogenesis during pregnancy [63,64].

❖ New born baby

Early vascular development and organ maturation in neonates depend on adequate feeding. Breast milk and new born foods contain ingredients like DHA (docosahexaenoic acid), which support angiogenesis and brain development in general. Additionally, vascular function may be hampered by vitamin or essential fatty acid shortages, which can result in problems like retinopathy of prematurity (ROP) in premature children [65,66].

❖ Old age people

The formation of new blood arteries is frequently hindered in older persons, which can lead to peripheral arterial disease (PAD), hypertension, and atherosclerosis. It has been demonstrated that diets high in bioactive substances including omega-3 fatty acids and flavonoids (such as resveratrol and quercetin) enhance angiogenesis by promoting blood vessel repair, decreasing inflammation, and boosting endothelial function. This can lower the risk of heart attack, stroke, and other circulation problems while also enhancing general cardiovascular health [67]. The body's capacity to heal wounds and regenerate tissues diminishes with age. A decrease in angiogenesis, which prevents the development of new blood vessels required for efficient healing, is partially to blame for this. Vitamin C, zinc, and polyphenols—found in foods like berries, dark chocolate, and green tea—are among the nutrients that are crucial for stimulating angiogenesis, which in turn speeds up tissue regeneration and wound healing in older adults. Angiogenesis's enhanced blood flow speeds up the healing process following surgeries, wounds, and other tissue injury [68]. Reduced angiogenesis in the brain is frequently linked to age-related cognitive decline, which can result in diminished blood flow and neurovascular dysfunction. Foods high in flavonoids from fruits and vegetables, omega-3 fatty acids (like fish oil), and antioxidants (like vitamin C and E) can promote angiogenesis in

the brain, supporting cognitive function and possibly lowering the risk of neurodegenerative diseases like Parkinson's and Alzheimer's. These nutrients ensure improved brain health as people age by promoting neuroplasticity and neurogenesis [69,70].

Discussion and Future Perspectives

As demonstrated by the previously described research, a therapeutic diet frequently has a positive regulating influence on angiogenesis. They can be utilised to treat angiogenic illnesses such tumours and cardiovascular disorders by increasing and blocking the transmission of various signals associated to angiogenesis. Throughout the 20th century, there has been a lot of emphasis focused on two conditions: tumours and cardiovascular and cerebrovascular illnesses. Studies on these have historically mostly concentrated on vasodilators and anti-cancer medications. Clinical investigations have revealed that both medication types have some clinical drawbacks, such as drug resistance, an ambiguous window of therapy, and a dearth of reliable biomarkers. Furthermore, prolonged human usage of these medications may result in the development of drug dependency and resistance [71]. When it comes to natural chemical compounds, therapeutic food is safer and more palatable than traditional medication, and its constituents are also more dependable. As a result, the function of food in controlling angiogenesis in the treatment of disease has received a lot of attention since the initial discovery that medical food and its active substances had a good regulatory influence on angiogenesis. The angiogenic regulating function of active substances in therapeutic meals has progressively come to light as research has progressed. In order to employ active substances in meals to mediate their angiogenic impact, it is crucial to comprehend the pathophysiology and regulatory mechanism of angiogenesis. Additionally, this will help provide a strong basis

for the investigation and creation of medicinal medications for vascular illnesses. As research progresses, angiogenic substances can now be used to mediate their angiogenic effects through the use of active components in food. This will also help as the regulatory impact of medical foods' active components has been progressively made public. As a result, knowing the pathophysiology and regulation mechanism of angiogenesis is crucial for providing a strong basis for the study and creation of therapeutic medications for vascular illnesses that are based on the properties of therapeutic foods and their active constituents. Medicinal foods and their active components can control angiogenesis and be used directly to cure angiogenic illnesses, according to some experimental research. They also offer a wide range of potential uses in the study, creation, and manufacturing of medications or other health items that regulate angiogenesis. The information that is now accessible has significant limitations, despite the fact that using medicinal foods and their active constituents to treat vascular illnesses is safer than using standard drugs. First off, there is now no oversight over follow-up clinical trials and other investigations; experimental research is restricted to the production of animal experimental models in the lab or simple pharmacological activity assays. Secondly, there is a glaring lack of study on the active components in medical foods. Numerous studies have demonstrated that food's active components can control angiogenesis, but none have established a dosage. Even though the right dosage is crucial, most studies only show a specific dose range, and the measurement is not consistent. The third is the system that controls therapeutic meals and the components that make them active in Angiogenesis is not clear.

Conclusion

It has been shown that certain diet elements and nutraceuticals can either preserve vascular structure and function or, in the end, stimulate the

development of capillary-like structures (by promoting the proliferation, migration, and invasiveness of endothelial cells). However, a large number of nutraceuticals, most of which are derived from plants, have the ability to suppress the angiogenesis-related processes that result in the regression or inhibition of vascular growth. It is important to remember that the same substances, or groups of substances, have both pro- and antiangiogenic effects. This seeming contradiction may be clarified by taking into account the milieu in which the active metabolites function, which is one in which reactive species and inflammation coexist and contribute to the development of illness in addition to the dysregulation of angiogenesis. In fact, the majority of the nutraceuticals that have been researched to far have anti-oxidative and/or anti-inflammatory effects.

As was previously said, the dual effect of a single nutraceutical on angiogenesis appears to be concentration- or dose-related. For example, red wine polyphenols have been shown to stimulate angiogenesis at low doses while acting as antiangiogenic agents at high levels through various cellular and molecular pathways. Vessel normalisation is an element that is conspicuously absent from the research about the impact of nutraceutical compounds on angiogenesis. It is crucial to have mature or physiological vasculature for both angio-inhibition and angiogenesis promotion, avoiding aberrant neovascularisation and extremely permeable/dysfunctional vessels. The impact of nutraceuticals on this characteristic has only been the subject of one experimental report: pre-treatment with neem leaf glycoprotein led to vascular normalisation in mice carrying melanoma and carcinoma, which also resulted in immunomodulation. This characteristic should be investigated in a more concise manner.

In summary, dietary active ingredients have the potential to be developed into effective interventional tools, but there are still a number of

critical issues that need to be resolved. These include enhancing our understanding of the concentration-mediated effects of dietary active ingredients, assessing the impact of particular active molecules and circulating metabolites, creating suitable formulations, and ultimately proving their efficacy as proangiogenic or antiangiogenic agents that can be used either on their own or in conjunction with medications.

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